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Effect of different DMARD use on the frequency of urinary infection in patients with rheumatoid arthritis

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ABSTRACT

Aims: It is known that the susceptibility to infection in general is increased in Rheumatoid Arthritis (RA) patients, but there is not enough information about whether urinary tract infections in particular differ according to different disease-modifying antirheumatic drugs (DMARDs) groups. The aim of this study was to compare the frequency of urinary infection attacks and pathogens in urine cultures of patients with RA treated with different groups of DMARDs.

Methods: In this retrospective study, 76 patients using biologic DMARDs (bDMARDs) and 74 patients using conventional synthetic DMARDs (csDMARDs) among patients followed with a diagnosis of RA for at least 5 years who came for regular follow-ups at our department's rheumatic diseases outpatient clinic were included. Patients with known immunodeficiency conditions, use of prednisolone (>7.5 mg), chronic renal failure, and renal pathologies were excluded from the study. The evaluation and follow-up records of the included patients between 01.01.2019 and 31.12.2022 were examined. Patients age, sex, medications, comorbidities, urine biochemistry, and urine culture results were recorded. Patients with pyuria detected by urine biochemistry were considered to have a urinary infection.

Results: The mean age of patients in the csDMARD group was 61.39±11.41 (37-87) and the mean age of patients in the bDMARD group was 58.68±11.42 (33-89) (p=0.149). The number of urinary infection attacks during the follow-up period was similar in both the groups (p =0.090). The positive culture rate was 23.21% in the bDMARD group and 7.5% in the csDMARD group (p = 0.072). *Escherichia coli* was detected in 81.8% and *Pseudomonas aeruginosa* was detected in 18.2% of the positive cultures in the bDMARD group. The pathogen in all positive cultures of the csDMARD group was *Escherichia coli*.

Conclusion: Although urinary infection and positive culture rates were higher in patients receiving bDMARDs, no statistically significant difference was observed between the groups.

Keywords: Rheumatoid arthritis, urinary tract infections, DMARD

INTRODUCTION

Rheumatoid arthritis (RA) is a common systemic autoimmune disease characterized by autoantibody production and chronic synovial inflammation.[1] Patients with RA have an increased risk of infection compared to the general population.[2] These infections are considered to be the main cause of morbidity and mortality in RA.[3]

As soon as patients are diagnosed with RA, disease-modifying antirheumatic drugs (DMARDs) should be started.[4] DMARDs are medications used to induce remission by suppressing autoimmune activity and slowing or preventing joint degeneration. These drugs are categorized as conventional synthetic DMARDs (csDMARDs), biological DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs).[5] Methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine are examples of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) that constitute a diverse class of medications. They are typically recommended as the initial treatment for individuals with RA.[4,5] If the initial treatment is either intolerable or ineffective, the recommendation shifts towards biological disease-modifying antirheumatic drugs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs).[5] bDMARDs target key components of the host immune defense system, such as tumor necrosis factor-α (etanercept, infliximab, golimumab, adalimumab, and certolizumab pegol), Interleukin-1, Interleukin-6 (tocilizumab) B cells (rituximab), and T cells, explaining the increased susceptibility of patients to certain types of infections.[6] Glucocorticoids (GCs) can be used as a bridge therapy in the treatment of RA until the effects of DMARDs begin or

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as adjunctive therapy for active RA that persists despite the use of DMARDs.[5]

There is an increased risk of infection compared with csDMARDs due to the immunosuppressive nature of bDMARDs.[6] Respiratory, soft tissue, and urinary systems were the most frequent sites of infection.[7] A cohort study by Cipriani et al.[9] included 731 patients using bDMARDs for rheumatic disease, and the most common site of non-serious infection was the urinary tract.[8] Urinary tract infections, which affect 150 million people worldwide each year, are among the most common bacterial infections.[9] The presence of clinical findings and an inflammatory response in the urinary system due to a pathogenic bacterium is defined as a urinary tract infection. Urinary system infections can present with very different clinical presentations, ranging from acute cystitis to acute complicated pyelonephritis.[10]

Although it is known that susceptibility to infection is generally increased in patients with RA, there is not enough information about whether urinary tract infections in particular vary according to the DMARD group used. Based on the hypothesis that bDMARDs increase the risk of infection, this study aimed to examine the frequency of urinary infections and causative pathogens in patients diagnosed with RA based on the drugs used.

METHODS

This study was approved by the Afyonkarahisar Health Sciences University (AFSU) Faculty of Medicine Clinical Researches Ethics Committee (Date: 07.04.2023, Decision No: 2023/164). In addition, prior to the study, permission to use the data was obtained from the Chief Physician of the Faculty of Medicine Health Application and Research Center (Hospital). Because the study was designed retrospectively, no written informed consent form was obtained from patients. The research was carried out in accordance with the principles outlined in the Declaration of Helsinki.

Patients who were followed up for at least 5 years at the Rheumatic Diseases Polyclinic of Afyonkarahisar Health Sciences University Faculty of Medicine Hospital, with a diagnosis of RA and using bDMARDs were evaluated. Patients with known immunodeficiency conditions, use of prednisolone (>7.5 mg), chronic renal failure, and renal pathologies were excluded from the study. 76 patients using bDMARDs and met the inclusion criteria were enrolled in this study. The control group included 74 patients using csDMARDs and meeting the inclusion criteria. The evaluation and follow-up records of the included patients between 01.01.2019 and 31.12.2022 were examined. Patients age, sex, medications, comorbidities, urine biochemistry, and urine culture results were recorded. Patients with pyuria detected by urine biochemistry were considered to have a urinary infection.[10]

Statistical Analysis

SPSS Statistics software (version 20.0; IBM Corp., Armonk, NY, USA) was used for statistical analysis. The Kolmogorov-Smirnov test was used to assess the distribution of continuous variables. Descriptive statistics were used to summarize the data, with n representing the number of units, % indicating the percentage, and median (minimum–maximum) values reported. Chi-Square test was used to compare categorical variables. The t-test was used to compare the means of two independent groups with normally distributed data, whereas the Mann–Whitney U test was used to compare the medians of two independent groups with non-normally distributed data. The statistical significance level was set at $p < 0.05$.

RESULTS

The mean age of patients in the csDMARD group was 61.39±11.41 (37-87) and the mean age of patients in the bDMARD group was 58.68±11.42 (33-89). Groups were similar in terms of age (p=0.149). The mean duration of biological agent use in patients using bDMARDs was 3.76±2.25 (1-9) years. Other demographic and clinical data of the patients are shown in **Table 1**. The distribution of drugs used by the groups is shown in **Figures 1** and **2**.

Table 1. Demographic and clinical characteristics of the groups

	csDMARD group (n=74) % (n)	bDMARD group (n=76) %(n)	p*
Gender Female/Male	74.3 (55)/25.2 (19)	71.1(54)/28.9(22)	0.653
Presence of comorbidity	59.5(44)	51.3(39)	0.316
GC use	66.2 (49)	15.8 (12)	<0.001

csDMARD conventional synthetic disease-modifying antirheumatic drugs, bDMARD biological disease-modifying antirheumatic drugs, GC Glucocorticoid, * Comparisons between groups chi square test

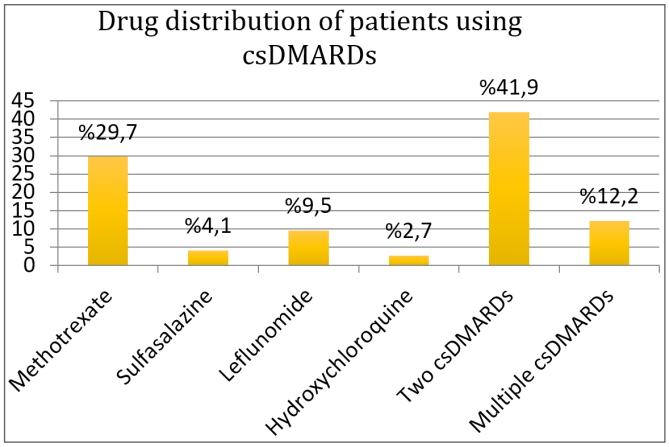

Figure 1. Drug distribution of patients using csDMARDs

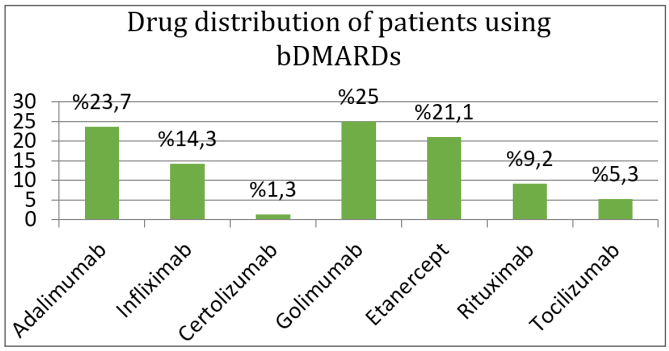

Figure 2. Drug distribution of patients using bDMARDs

Although a history of malignancy was more common in the csDMARD group (p=0.011), the groups were similar in terms of other comorbidities (p>0.05). The distribution of comorbidities in each group is shown in **Figure 3**.

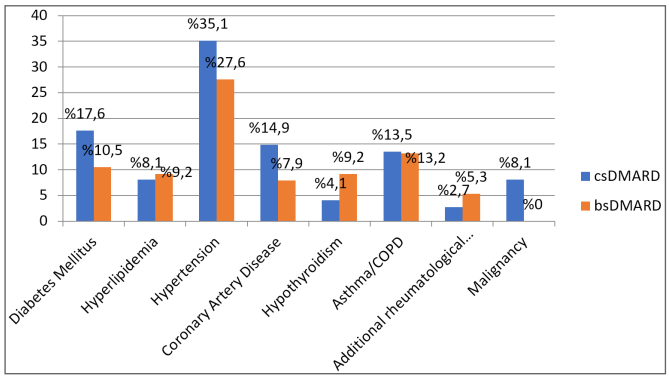

Figure 3. Comorbidities of the groups

Urine biochemistry analysis was performed at each admission during follow-up. The number of urine biochemistries analyzed in the 4-year follow-up in the csDMARD group was 6.96±4.53, while it was 8.97±8.18 in the bDMARD group (p=0,356). The number of urinary infection attacks during the follow-up period was similar (p = 0.090) (**Table 2**).

Table 2. Comparison of urinary infection frequency and positive culture rates between groups

	csDMARD group (n=74)	bDMARD group (n=76)	p
Number of urinary infection attacks Mean±SD (min-max)	1.50±2.16 (0-9)	2.42±4.15 (0-22)	0.090*
Positive culture rate (%)	7.5	23.21	0.072**

csDMARD conventional synthetic disease-modifying antirheumatic drugs, bDMARD biological disease-modifying antirheumatic drugs, SD standard deviation, min-max minimum-maximum, ** Comparisons between groups independent samples t-test, ** Comparisons between groups independent samples Mann Whitney U test.

The number of urine cultures examined during the 4-year follow-up in the csDMARD group was 0.56±0.87, while it was 0.67±1.18 in the bDMARD group (p=0,891). The positive culture rate was 23.21% in the bDMARD group and 7.5% in the csDMARD group (p = 0.072) (**Table 2**).

Escherichia coli (*E. coli*) was detected in 81.8% and *Pseudomonas aeruginosa* was detected in 18.2% of the positive cultures in the bDMARD group. The pathogen in all positive cultures of the csDMARD group was *E. coli*.

DISCUSSION

In this study, the number of urinary infection attacks in patients treated with biological agents was compared with that in patients receiving csDMARDs during a 4-year follow-up period. Although urinary infection and positive culture rates were higher in patients taking bDMARDs, the difference was not statistically significant.

Urinary infections are the second most common infections in RA after respiratory tract infections, as in all systemic autoimmune diseases.[11,12] Patients with autoimmune disorders are at significant risk for serious infections. This heightened vulnerability stems from alterations in immune function resulting from the underlying disease, which can compromise both the cellular and humoral immune responses. Additionally, the impact of immunosuppressive therapies employed to manage disease activity further contributes to increased susceptibility to infections.[13]

Patients with rheumatoid arthritis (RA) have an increased risk of infections due to factors such as older age, extra-articular disease, high disease activity, presence of chronic obstructive pulmonary disease, interstitial lung disease, chronic kidney disease, lymphopenia, use of glucocorticoids (GC), and utilization of disease-modifying antirheumatic drugs (DMARDs).[11] In their cohort study by Cipriani et al.[8] 731 patients were examined using bDMARD for rheumatic disease, and disease duration, longer follow-up period, concurrent steroid treatment, and comorbidities were found to be significantly associated with non-serious infection.[8] In our study, risk factors such as follow-up periods and comorbidities of patients using bDMARDs and csDMARDs were similar; however, the rate of GC use was higher in the csDMARD group. This may have affected the results of our study and acted as an additional risk factor for patients using csDMARDs. Sharma et al.[14] reported that age and the duration of bDMARD use were significant factors associated with an increased risk of serious infections.[14]

The most commonly used bDMARDs are TNF-α inhibitors. TNF-α plays an important role in the pathogenesis of RA.[15] These drugs are used to treat RA, especially in patients whose disease does not respond to treatment with csDMARDs.[16] The prognosis of patients with RA has significantly improved with the use of TNF-α inhibitors, but these drugs, which target key molecules involved in the immune response to infectious agents, may also increase susceptibility to viruses and bacteria and cause adverse effects.[17]

In a review examining the infection profile in patients taking biologic drugs, lower respiratory tract, ear/nose/throat, and urinary infections were found to be moderately common and were particularly clustered in patients taking TNFα inhibitors.[18] Similar infection risks have been shown to exist with non-TNFα inhibitor bDMARDs such as rituximab and tocilizumab.18 In a study by Quach et al.[19] infections occurred less frequently in patients receiving hydroxychloroquine in addition to sulfasalazine and methotrexate treatment than in patients receiving etanercept + methotrexate.[19] Analysis of real-world and clinical trial data from patients with RA has shown an increased risk of serious and non-serious infections in patients taking bDMARDs compared with csDMARDs.[20] In fact, etanercept, a TNF-α inhibitor, has been reported to have a lower risk of infection than other TNF-α inhibitor agents and the Janus kinase (JAK) inhibitor tofacitinib from the tsDMARD group.[20] Similarly, in a study by Yun et al.[21] among rheumatoid arthritis patients who had an infection in the hospital during TNF-α inhibitor treatment, abatacept and etanercept had the lowest risk of subsequent infection compared to other biologic treatments.[21]

In a prospective observational cohort study conducted by the British Society of Rheumatology Biological Rheumatoid Arthritis Register, several factors were associated with an increased risk of infection. These included advancing age, female gender, higher comorbidity burden, the use of glucocorticoid therapy, elevated Disease Activity Score in 28 joints, and a higher Health Assessment Questionnaire disability index. Notably, the study revealed a significant decrease in the risk of infection with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) compared to biological treatments. Within the biological treatment category, the study identified variations in infection risk. Tocilizumab and rituximab were associated with a higher risk of infection, while the csDMARD cohort showed a lower risk. Among the TNF-α inhibitors, adalimumab was linked to a higher risk of infection than etanercept. This information provides valuable insights into the factors influencing infection risk in patients with rheumatoid arthritis, helping to guide treatment decisions and patient management strategies.[22] Several recent studies have shown that the risk of infection differs between the top three TNF-α inhibitor agents: infliximab increases the risk compared with etanercept or adalimumab.[23] Based on these results, the fact that the majority of our patients were using golimumab, adalimumab, and etanercept may explain the lack of an increased risk compared with csDMARDs.

A meta-analysis of randomized controlled trials examining rituximab did not show a significant increase in the risk of infection. Similarly, in a separate meta-analysis that focused on tofacitinib, there was no elevated risk of infection associated with its use.[23]

Although there are studies in the literature showing that bDMARDs increase the risk of infection, some studies have shown that some biologics do not increase the risk. According to the results of this study, despite the small sample size, we can infer that bDMARDs do not significantly increase the risk of urinary infection compared with csDMARDs. The heterogeneity of the bDMARD molecules used in our patients may have affected our results. In addition, the higher GC use rates in our csDMARD group may explain why urinary infection rates in patients using csDMARDs were similar to those in patients using bDMARDs. Glucocorticoids have the potential to hinder phagocyte function and suppress cell-mediated immunity, thereby contributing to increased susceptibility to infections. A meta-analysis based on randomized clinical trials and observational studies showed an increased relative risk in patients with RA with a positive dose-response effect in GC users.[23] Although the use of csDMARDs seems to be more innocent in terms of infection compared to bDMARDs, it should be taken into consideration that GC use is more common in patients using csDMARDs, and caution should be taken in terms of urinary infections in patients using csDMARDs.

Urinary infections can be caused by both Gram-negative and Gram-positive bacteria as well as by some fungal agents. The most common cause of both uncomplicated and complicated urinary infections is uropathogenic *Escherichia coli*.[24] In addition, *Klebsiella pneumoniae*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, group B *Streptococcus*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida* species may be the causative agents.[9] Eighty precent of tract infections in healthy women aged 18-39 are caused by *Escherichia coli*.[21] In a Spanish registry study, the National Drug Safety Registry of Patients with Rheumatic Diseases reported that cystitis was mainly caused by *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella pneumoniae*.[25] Similar to previous studies, the most common agent in our study was *Escherichia coli*.

Limitations

Since our study was retrospective, other risk factors such as duration of bDMARD use, antimicrobial use, and hospitalization history were not investigated, and disease activities were not examined. In addition, the small sample size is another limitation because this was a single-center study.

CONCLUSION

The findings of this study indicate that the incidence of urinary tract infections among patients receiving bDMARDs was similar to that of patients receiving csDMARDs over a four-year observation period. It is imperative to exercise caution regarding the potential for urinary tract infections when utilizing bDMARDs, as evidenced by the current body of literature. In addition, it is essential to closely monitor patients who are on csDMARDs for any signs of urinary tract infections, particularly when they are using additional GC.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Afyonkarahisar Health Sciences University (AFSU) Faculty of Medicine Clinical Researches Ethics Committee (Date: 07.04.2023, Decision No: 2023/164). In addition, prior to the study, permission to use the data was obtained from the Chief Physician of the Faculty of Medicine Health Application and Research Center (Hospital).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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